Xenografting: ethical issues

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Abstract
This paper considers the ethical issues raised by xenotransplantation under four headings: interfering with nature; effects on the recipient; effects on other humans; and effects on donor animals. The first two issues raise no insuperable problems: charges of unnaturalness are misguided, and the risks that xenotransplantation carries for the recipient are a matter for properly informed consent. The other two issues raise more serious problems, however, and it is argued that if we take seriously the risk of transferring new infectious agents from animal to human populations and the interests of donor animals, then a moratorium on xenotransplantation is called for. The paper finds that the recent Nuffield Council and Department of Health reports on xenotransplantation are insufficiently cautious in the conclusions that they draw from these considerations. (Journal of Medical Ethics 1998;24:18–24)

Keywords: Xenograft; xenotransplantation; animal welfare

The idea of using animals as a source of organs for transplant into humans has been around for some time, but until now these procedures have been bedevilled by problems of immune system rejection: few patients have survived more than a few weeks and many have died in a matter of hours or less. Recently, however, there has been an upsurge of interest, resulting from technological developments that offer improved prospects for xenograft recipients. Better immunosuppressive drugs may help to reduce the rate of rejection, particularly with organs from closely related species such as baboons, and genetic modification of donor animals (particularly pigs) may improve their organs’ compatibility with human recipients and hence reduce human immune system responses.

The ethical arguments in favour of continuing this research and developing treatments are clear and need little explanation. Although it is possible that xenotransplantation will become the medically preferred treatment for some conditions, the main consideration prompting current interest is the shortage of donated human organs. Xenotransplantation, it is hoped, will close the gap between the number of patients in need of transplanted organs and the number of organs available. The moral importance of treating more patients and of finding better treatments should be uncontroversial, so I will not analyse these motivations any further. I am not assuming, however, that these are the only considerations motivating the development of xenotransplantation, for it is clear that the financial incentives for companies to become involved in the development and supply of xenotransplantation technology are huge. What I am assuming is simply that the considerations I have cited provide sufficient reasons for developing xenotransplantation in the absence of countervailing considerations. The question to be answered, therefore, is whether xenotransplantation is an acceptable means of achieving those ends.

The ethical problems raised by xenotransplantation will, in this paper, be considered under the following headings: (i) interfering with nature, (ii) effects on the recipient, (iii) effects on other humans, and (iv) effects on donors. Other classifications could be used, but this one has been chosen in order to highlight the differing ethical status of considerations falling under each of these categories. In exploring these issues it will be argued that although the recent reports for the Nuffield Council on Bioethics and the Department of Health have made important contributions to this debate, both reach conclusions that are insufficiently cautious in the light of the problems that they address.

1. Interfering with nature
The idea that transferring organs from animals to humans is unnatural probably explains a great deal of the disquiet that many people feel about such procedures. Explanations, however, are not always vindications, and in this case objections to “interfering with nature” or “playing God” (to use a related and oft-heard expression) are misplaced.

Aside from xenotransplantation, charges of unnaturalness are often heard in arguments about sexual morality and the related medical field of assisted conception and reproduction. The claim is that certain acts or treatments are unnatural, and therefore wrong. However, it is notoriously
difficult to define what is natural and what is unnatural. On one account everything that humans do is by definition unnatural, because it constitutes an interference with the non-human natural order. On this account we cannot avoid interfering with nature, so the suggestion that one course of action is unnatural cannot be a reason for doing something else instead. On another account nothing that humans do is unnatural, since humans are themselves a part of nature. If nothing we do is unnatural then nothing we do can be unnatural and therefore wrong. It might be thought that these are extreme views on what constitutes the natural, and that what is required is the drawing of an intermediate line, dividing human actions into the natural and unnatural. The problem, however, is that it is very difficult to find a clear and well-motivated place in which to draw such a line, and even if such a line were drawn, it is not at all clear that the kinds of medical treatment condemned as unnatural, such as artificial conception and xenografting, would fall on one side, with more widely accepted treatments such as the use of antibiotics on the other. Indeed, the fact that a proposed boundary would divide medical treatments in this way might well be taken as a reason for regarding the line as an arbitrary one.

"Natural" facts

A second problem with the condemnation of "unnatural" procedures is that even if we can distinguish what is natural from what is not, it is unclear why we should prefer the former and regard interference with nature as wrong. John Stuart Mill famously opposed this view by pointing out that nature's powers "are often towards man in the position of enemies, from which he must wrest by force and ingenuity, what little he can for his own use". It is only by interfering with nature that we can free human lives from the destructive effects of such natural phenomena as infectious agents, droughts and hurricanes.

Nevertheless, the distinction between the natural and the unnatural seems important to many people, and an explanation of this has recently been proposed by Richard Norman. His suggestion is that we need a background of "natural" facts—facts that we think of as beyond our control—in order to give meaning and value to our choices. It is because of the enduring reality of human sickness and pain, aging and death, that attempts to prevent or mitigate these evils in particular cases have meaning. We may aim for a world without pain, but if we achieved it certain valuable kinds of action would cease to be possible, and if there were no facts of life beyond our control then our lives would lack the structure that makes the idea of choice intelligible. Environmental ethicists have similarly argued that wilderness areas, created by natural processes and unchanged by human agency, are to be valued for providing us with a "larger context", something "outside of ourselves", in which to situate the plans and projects that comprise our lives. However, while the need for a background against which to locate our choices and actions may explain our attachment to an idea of the natural, it does not provide us with a reason to reject procedures such as IVF or xenografting.

Human biology

The charge of unnaturalness in relation to IVF and related procedures is prompted by the fear that such developments (like the use of contraception according to Roman Catholic teaching) will destroy the connection between sex and procreation which gives sex its particular significance, but as Norman points out, these developments are very far from destroying that connection at a general level. Similarly it might be suggested that xenografting will destroy the way in which human lives are structured by their dependence upon the particular characteristics and limitations of human bodies. Once again, however, the fear is overstated: our lives are structured by the nature of our bodies, but a part of that structure consists of the incentive that we have to struggle against particular limitations. Xenografting, along with other medical procedures, is one of the means by which we may pursue that struggle, and even if it were to become a successful and widespread form of treatment we would be a long way from putting the struggle behind us and severing our dependence upon human biology.

Another worry about naturalness, raised by the Nuffield Report, concerns the way in which a patient's self-image might be affected by xenotransplantation:

"One cause of unease is the breaching of normally inviolate boundaries. This is seen in human organ transplantation. The recipient of a transplanted organ may feel that the boundary between self and non-self has been breached. ... With xenotransplantation, an additional boundary, that between human and animal, may become blurred."

The force of this point is that the worries described may be a real source of harm to recipients of animal organs, irrespective of whether the worries are well-grounded. In the light of my previous comments we may judge it irrational to regard receipt of a xenograft as a dilution of one's humanity, or to regard it as being qualitatively
different from the use of human organs, prosthetics or any other medical modification of the human body. It may therefore be that discussion of these issues in the course of counselling will cause such worries to disappear. On the other hand the worries may remain, despite counselling and despite the lack of a rational grounding, causing serious detriment to a patient's wellbeing. If this proves to be the case, then it is a real objection to xenotransplantation, at least in patients thought prone to such worries. However, this is not fundamentally an objection based on the unnaturalness of xenotransplantation (since the objection is independent of the truth of that charge), but one which properly belongs with the next set of problems to be considered, problems arising from the detrimental side effects (in this case the psychological side effects) that xenotransplantation may have upon the recipient.

2. Effects on the recipient
In any medical decision, the benefits that the patient stands to gain from a treatment must be balanced against its risks. Given the experience of xenotransplantation to date, the risks to recipients of animal organs must be considered very substantial. One kind of risk—the risk of psychological damage associated with a changed self-image—has already been mentioned, but the main risks to xenograft recipients are the risk of rejection, the increased risk of infection resulting from immunosuppression, and the risk of diseases transmitted from the donor animal. None of these risks is unique to xenotransplantation, all being problems for human organ transplants as well, though the first two risks are likely to be greater in the case of xenotransplantation: the risk of rejection is higher, and consequently higher levels of immunosuppression are likely to be needed. The risk of disease transmission is hard to quantify, a point which I will return to in the next section.

The main ethical issue raised by these risks is that of consent. It is vital that potential patients are made aware of the risks before agreeing to the treatment, but so long as only the patient's interests are at stake, and the patient is fully aware of the potential benefits and risks of treatment, the patient's autonomous decision ought to determine his or her treatment. This assumes that the patient is capable of making an autonomous choice, and for this reason both the Nuffield and Department of Health reports recommend that early xenografts should be given only to competent adults. It is also necessary to ensure that the patient's decision is freely made, and to safeguard this the reports recommend that patients who refuse xenografts should remain eligible for human organs on the same basis as before.10

I have suggested that as long as the choice of treatment affects only the interests of the patient, the patient's choice should be respected. This view, however, is not universally shared. It is held by some that there are limits to what people should be allowed to consent to. It might be argued, for example, that the prospects for xenograft recipients are at present so poor that it would be wrong to carry out further procedures even with the recipients' full consent. The most plausible basis for this view is that there are some risks that it cannot be rational to accept—and that the fact that a patient does consent to them is evidence that he is desperately clutching at straws and incapable of making a rational choice. But who is to say that it is irrational for a patient in a desperate situation to accept desperate odds? Acceptance of high risks may indicate an impaired capacity to make rational choices, but judgments of a patient's competence must be made on more than this evidence alone.

Another putative reason for limiting what people are allowed to consent to arises when we consider the experimental nature of current xenotransplantation procedures. At present the prognosis for xenograft recipients is very poor, but it is hoped that this will improve as experience is gained, as has happened with human organ transplants. The danger here is that patients will be encouraged to accept greater risks than would usually be judged in their interests, for the benefit of future patients. This possibility clearly reinforces the need to ensure that patients are properly informed before agreeing to participate, and that their consent is freely given, but there is also a widely held view that patients should not be permitted to consent to participation in medical trials unless it is judged that there is a reasonable prospect of their benefiting from the treatment. This is a controversial view since, on the face of it, it appears to prohibit heroic altruism12; however, I merely wish to note here that what makes experimental treatments controversial is the fact that it is not only one person's interest at stake: the risks and benefits may accrue to different people, allowing the prospect of one person's interests being sacrificed for the benefit of another.

3. Effects on other humans
The separation of risks and benefits becomes clearer when we consider the next set of ethical problems raised by xenotransplantation: the effects on humans other than the recipient. The most important issues here are the risk that diseases transmitted from animals to humans may
prove infectious between humans, leading perhaps to new AIDS-type epidemics, and the costs that will be borne by other patients if resources are redirected from other areas of medical research and treatment to fund xenotransplantation. The fact that xenotransplantation carries risks not just for the xenograft recipient but for the population generally is important because it takes the ethics of xenotransplantation outside the realm of individual consent and into the realm of justice, raising questions about the extent to which it is permissible for an individual to impose risks on others for his own benefit.

The issue of reallocating resources is not specific to xenotransplantation, but raises the same problems as the introduction of any other new and experimental treatment—problems of predicting future costs and benefits and of ensuring effective and equitable use of resources. The question here is whether xenotransplantation would be a better or worse use of resources than the available alternatives.

**More serious problem**

The risk of transmitting infectious diseases to the wider population, however, is an altogether more serious problem. We do accept the imposition of some risks on others for our own benefit (for example when we drive cars). However, there are limits to what we regard as acceptable (it is not acceptable, for example, to drive when drunk), and it is therefore necessary to consider the nature of the risk imposed on the wider population by xenotransplantation procedures. The difficulty for proponents of xenotransplantation is that the worst-case scenario (a major new epidemic) is extremely grave, and its likelihood is difficult if not impossible to quantify. As the Nuffield report explains:

"It will be very difficult to identify organisms that do not cause any symptoms in the animal from which they come. Previous experience indicates that infectious organisms are normally identified only after the emergence of the disease they cause.

... Put bluntly, it may be possible to identify any infectious organism transmitted by xenografting only if it causes disease in human beings, and after it has started to do so.""12

Moreover, if, as in the case of HIV, there is a long incubation period between infection and development of the disease, the agent may have spread far beyond the original xenograft recipient by the time its symptoms are noticed, undermining any hope of containing the infection. The Nuffield report concludes from these considerations that the risk of a major epidemic is unquantifiable, and in the light of this advocates a precautionary principle, requiring "that action should be taken to avoid risks in advance of certainty about their nature" and that "the burden of proof should lie with those developing the technology to demonstrate that it will not cause serious harm".14

Unfortunately, the measures that the report proposes in order to safeguard against disease transmission do not live up to this principle.

The report begins robustly enough, by stating:

"that the risks associated with possible transmission of infectious diseases as a consequence of xenotransplantation have not been adequately dealt with. It would not be ethical, therefore to begin clinical trials of xenotransplantation involving human beings".15

However, the report goes on to suggest that xenotransplantation should be allowed to proceed once the following conditions have been satisfied: (1) that "as much information as possible" be assembled about the risks of transmission; (2) that source animals be "reeled in conditions in which all known infectious organisms are monitored and controlled"; (3) that early recipients undergo regular monitoring and testing; and (4) that there be "a commitment to suspend, modify or, if necessary, discontinue xenotransplantation procedures at any signs that new infectious diseases are emerging". These precautions, however, are far from watertight, for, as noted above, the report acknowledges that full knowledge of potentially ineffective agents is for all practical purposes impossible. A consequence of this is that source animals cannot be freed from all infectious organisms but only those that are known and can be reliably tested for: "Specified pathogen-free animals may still be infected with unidentified infectious organisms about which nothing is known".16

Because the risk of disease transmission cannot be eliminated, the report recommends that procedures for monitoring of recipients be established and that consent to this be included in consent to the xenograft. Monitoring, however, is of no use unless backed-up by a plan of action, and as the following passage demonstrates, the report fails utterly to provide such a plan.

"The most difficult question is what procedure should be followed if it is found that a disease has indeed been transmitted from the animals used to provide organs or tissue to human xenograft recipients? In principle, steps should be taken to prevent transmission of the disease to other people. In practice, this is a very difficult issue. For a start, it is very unlikely that, at the outset, the mode of transmission of the disease will be
understood. The appropriate response will depend on the mode of transmission and on how infectious the disease is. It would hardly be acceptable to isolate xenograft recipients suffering from an infectious disease, or to ask them to refrain from sexual intercourse or, in the case of a virus transmitted from parent to offspring, from having children. This highlights how difficult it would be to prevent the transmission of an infectious disease originating from xenotransplantation. It is sobering to reflect on the difficulty, despite globally coordinated attempts, of controlling and eliminating infectious diseases such as malaria, hepatitis and AIDS.17

This is indeed a sobering passage, and given such pessimism about the prospects for containment of any new infection, the precautionary principle would appear to require that the proposed moratorium on xenotransplantation procedures be made indefinite.

The Department of Health report goes further than the Nuffield report in discriminating the risks posed by different kinds of infectious agent, but reaches similar conclusions. Fungi, parasites and bacteria, it concludes, pose relatively little risk either to the xenograft recipient or to the wider population.18 With regard to prions, it holds that transmission to xenograft recipients is unlikely (though recent controversy about the transmissibility of prion disease from BSE-infected cattle to humans might lead us to doubt the reliability of scientific advice on this matter), and that prions are unlikely to be transmitted from one human to another. In view of the latter, the long incubation period typical of prion disease appears as an advantage rather than a disadvantage, allowing that even an infected recipient may benefit from years of good quality life, without posing a risk to others.19 The greatest risk, the report concludes, is from viruses, due to their transmissibility between humans, the long incubation periods of some viral infections, and our limited ability to screen for and exclude known and unknown viruses in donor animals. As far as viruses are concerned, the Department of Health report concurs with the Nuffield report that the risk of infection and onward transmission is at present too great to justify experimental procedures.

**Future acceptability**

Unfortunately the Department of Health report runs into the same difficulties as the Nuffield report in considering the future conditions under which xenografting might become acceptable. It too premises the future acceptability of xenotransplantation upon the hope that further research may show the risk of infection to be “within tolerable margins”, while acknowledging that it cannot ever be totally ruled out.20 In expressing this hope, however, the report ignores the difficulty, raised by the Nuffield report, of quantifying, and assessing as tolerable, a risk posed by agents that are as yet unidentified. The Department of Health report also follows the Nuffield report in advocating monitoring of xenograft recipients as a further safeguard against the spreading of infections and, again, like the Nuffield report, offers no satisfactory account of what should be done in the event of a positive result, suggesting only that “appropriate additional research” may be indicated.21

**4. Effects on donor animals**

So far I have considered the ethics of xenotransplantation in terms of its significance for humans, but of course much of the controversy surrounding this issue arises from concerns about the imposition of harms upon non-humans for human benefit. Like the non-recipient humans at risk from transmitted diseases, the donor animals are non-consenting parties who stand to be harmed by a procedure designed to benefit others. In the case of animals, however, a greater degree of imposed sacrifice is widely held to be acceptable. The problem for advocates of xenotransplantation is to justify this intuition and to quantify the degree of sacrifice that may plausibly be imposed.

One way of addressing the latter would be to look at other ways of treating animals about which we have clear views, and to ask whether the use of animals in xenotransplantation is more or less acceptable than these. For example, we might conclude that if it is acceptable to raise and kill animals for food, then it must be acceptable to raise and kill them for medical purposes, since eating meat is a luxury whereas xenotransplantation and medical research are often matters of life and death. A weakness in this argument is that we are not all agreed on the acceptability of eating meat, so the method is unlikely to generate an agreed conclusion. Moreover, even if we assume agreement on the acceptability of meat consumption, the comparison between this and xenotransplantation may not be as straightforward as it seems, since xenotransplantation is likely to introduce particular animal welfare problems that are not present (or not necessarily present) in the raising of animals for food. For example, the need to keep donor animals free (as far as possible) from infectious agents may require them to be raised in isolation, and the genetic modification necessary to achieve compatibility with humans may impair health and cause suffering in the
donor animals. And, in addition to the donor animals themselves, significant numbers of animals will be needed as experimental subjects in order to develop the necessary genetic manipulation and transplantation techniques, and to investigate the dangers of disease transmission. It follows, then, that since the animal harms as well as the human benefits of xenotransplantation may be greater than those of meat-eating, a simple inference from the permissibility of the latter to the permissibility of the former will be invalid. A different approach is therefore needed in order to justify the sacrifice of animal interests required by xenotransplantation procedures.

Mental capacities
Justifications for both medical and culinary uses of animals typically appeal to the different mental capacities of humans and other animals. Imposing harms on animals in order to benefit humans is acceptable, it is argued, because the harms and benefits that humans are capable of experiencing are greater than those that can be experienced by other animals. The physical pains suffered by animals, according to this argument, are less significant than those suffered by humans, because animals are less sensitive, or because they lack the capacity for fearful anticipation or distressing memory which amplify the effects of physical pain in humans. And death matters less for animals, it is argued, because animals have less to lose than humans in the form of potential for future pleasures and satisfactions, or because the loss of these things matters less to creatures who lack our capacity to foresee, desire and plan for them. Both the Nuffield and Department of Health reports appeal to arguments of this kind in order to justify xenotransplantation, citing the different capacities of different species in support of the view that it is acceptable to use pigs, but not primates, as xenograft donors:

“When considering the use of primates for xenotransplantation, the capacities they share with human beings, notably their self-awareness, led to ethical concerns about their use for xenotransplantation. While unquestionably intelligent and sociable animals, there is less evidence that pigs share capacities with human beings to the extent that primates do. As such, the adverse effects suffered by the pigs used to supply organs for xenotransplantation would not outweigh the potential benefits to human beings”.

Unfortunately for the reports, this kind of argument is vulnerable to a well-known objection. The problem is that capacities for pleasure and pain, fulfilment and suffering vary not only between but within species, including humans. So while it is true that the capacities of a normal adult human exceed those of a pig, the same cannot be said for all humans. There are many whose mental capacities are severely and tragically impaired, and it follows that if we are prepared to take organs from animals on the grounds of their limited capacities we should also be prepared to take the organs of those humans whose capacities are similarly restricted. Or conversely, if we insist that we should not take organs from such humans, then consistency demands that we refrain also from taking the organs of animals with similar or greater capacities.

This point about the overlapping capacities of humans and other animals is most often advanced as an argument against the use of animals, in, for example, medical research. An exception, however, is its use by RG Frey, who suggests that experimentation on animals is too valuable to do without, and that we should therefore bite the bullet and accept the use of some severely mentally impaired humans as experimental subjects. Applied to xenotransplantation, Frey’s suggestion is that we should accept the killing of some mentally impaired humans for their organs rather than forgo the benefits of xenotransplantation. Now this, for many, will be too much to accept, and it will be held that we must do without vivisection or xenotransplantation if the only consistent alternative is to accept that mentally impaired humans as well as animals may be used for these purposes. Others will argue that even if we were to accept Frey’s stance in principle, the difficulties of measuring and comparing mental capacities across species would make it impossible to judge which humans should be used in preference to which animals. It may be, however, that among the possible ways of reforming our procedures for procuring human organs there are some which do not involve unacceptable human costs, and which can reasonably be judged to be morally preferable to xenotransplantation.

Opting-out system
I have in mind reforms which would increase the supply of organs from humans who lack any capacity for suffering, either because they are dead or because they have lost, or never had, any higher brain function. These reforms could include, firstly, a relaxation of the requirement for consent in obtaining organs from cadavers, by removing the relatives’ veto and moving to an opting-out system, with opt-outs perhaps restricted to those with a conscientious objection. Secondly, they could include relaxation of the whole-brain criterion of death, in order to allow removal of organs
from anencephalic infants and patients in persistent vegetative states. Although these proposals would involve only donors who are lacking consciousness and therefore incapable of being caused suffering, it might be objected that such measures would result in distress for other humans: relatives, onlookers, and other third parties. However, we would have to judge that animals’ interests matter very little indeed for the direct harm that xenotransplantation would impose on them to be outweighed by the third-party concerns of some humans. This is especially true when we consider that the use of animals would also be likely to cause distress amongst human onlookers, as a result of and in addition to the direct harms imposed on the animals, and that given the absence of any such direct harm in the human case, the third party distress factor would be likely to diminish as the new practices became more established.

The suggestion that measures for increasing the supply of human organs be explored before resorting to xenotransplantation is also supported by the arguments of the previous section, since it would avoid — or at least postpone — the risk of transmitting infectious diseases from animals to the human population. Whether such measures would be sufficient to close the organ gap is uncertain, but the conclusion to which we are led, if we take seriously both the interests of animals and the risks of disease transmission to humans, is that a moratorium should be imposed upon xenotransplantation procedures at least until possible avenues for increasing the supply of human organs have been exhausted and until a more reassuring judgment can be reached on the prospects for preventing and containing transmitted infections.

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References and notes

8 See reference 3§9.12. See also reference 4§7.14 for a more general comment on the psychological and social impacts of xenotransplantation on the recipient.
9 See reference 3§7.23, 7.25; reference 4§7.7.
10 See reference 3§7.30, 7.31; reference 4§7.15.
11 Perhaps for this reason the Department of Health report holds back from endorsing such a restriction. Its view appears to be that any trial conducted, considered as a whole, must offer the prospect of therapeutic benefit to patients, while leaving open the possibility that those trials may include volunteer participants in whose individual cases benefit is unlikely. See references 4§§7.5, 7.6.
13 In the words of the Nuffield report: “It is not possible to predict or quantify this risk but, in the worst case, the consequences could be far-reaching and difficult to control”. Reference 3§6.20.
14 See reference 3§6.21.
15 See reference 3§6.23.
16 See reference 3§6.30.
17 See reference 3§6.36.
18 See reference 4§4.54.
19 See reference 4§4.55.
21 See reference 4§§4.68, 4.63.
22 Similar statements can be found in reference 4§§4.28-4.30. Both reports, however, approve the use of small numbers of primates as recipients of organs from non-primates during research into xenotransplantation.
23 The best-known proponent of this argument as an objection to vivisection and other uses of animals is Peter Singer. See, for example, Singer P. Practical ethics. Cambridge: Cambridge University Press, 1993:65-8.
25 This could take the form either of a redefinition of death, or dropping of the requirement that patients be dead before removal of organs in favour of the requirement that they have permanently lost consciousness. The latter is recommended by Singer P. Rethinking life and death. Oxford: Oxford University Press, 1995.